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PATENT SPECIFICATION

NO DRAWINGS

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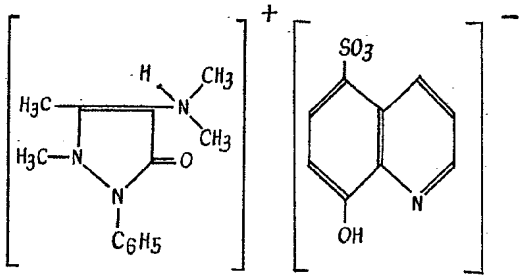
COMPLETE SPECIFICATION

Pyrazolone Derivatives and Pharmaceutical Compositions containing them

We, LABORATORIO CHIMICO FARMACEUTICO CAUSYTH S.P.A., an Italian Body Corporate, of Via Serio 6, Milan, Italy, do hereby declare the invention for which we pray that a patent may be granted to us and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to derivatives of 1,5 - dimethyl - 4 - dimethylamino- 2 - phenyl - isopyrazolone 8 - hydroxyquinoline - 5 - sulphonate and to pharmaceutical compositions containing them.

1,5 - dimethyl - 4 - dimethylamino - 2 - phenyl - 3 - isopyrazalone 8 - hydroxyquinoline - 5 - sulphonate is known under the Registered Trade Mark CAUSYTH and is hereinafter identified as CAUSYTH(R). It has the structural formula:



It is, as shown in clinical medical literature, a specific medicament in the therapy of influenzal and rheumatic conditions. In the maximum doses in which it is employed it is, practically speaking, free from caustic, toxic, sensitising and haemolytic effects and other secondary actions which would make it undesirable for use in the therapy of influenzal and rheumatic conditions and all febrile conditions in general.

Heretofore, CAUSYTH(R) has been used solely by the oral or rectal method but there are pathological conditions which make a therapy of attack and reinforcement by means of an aqueous solution of the product preferable. However this last-mentioned method of use has not previously been practicable by reason of the known insolubility of CAUSYTH(R) in aqueous media. In fact, CAUSYTH(R) appears to be practically insoluble in most aqueous solutions, although it is slightly soluble in aqueous alkaline solutions containing lithium, sodium, potassium, rubidium or caesium hydroxides. Such solutions are however generally strongly alkaline (having a pH of more than 11) and cannot be used parenterally.

It is an object of the present invention to provide an aqueous solution containing CAUSYTH(R) that is suitable for injection.

It has now been found that CAUSYTH(R) can easily be rendered soluble in water by formation of a complex between it and a polyhydroxyamine.

According to the present invention therefore there is provided a water-soluble complex of 1,5 - dimethyl - 4 - dimethylamino - 2 - phenyl - 3 - isopyrazolone 8-

[*Price 4s. 6d.*]

hydroxy - quinoline - 5 - sulphonate (CAUSYTH ®) and an aliphatic or aliphatic cyclic polyhydroxy-amine.

Preferably the polyhydroxy-amine is aminoglycerine, methyl - aminoglycerine, glucamine, methylglucamine, glucosamine or methylglucosamine.

By 'an aliphatic cyclic polyhydroxyamine' is meant a polyhydroxyamine containing a closed non-aromatic ring which may be a heterocyclic ring. Glucosamine and methylglucosamine in their cyclic forms are examples of aliphatic cyclic polyhydroxy-amines.

The complexes of the invention may be formed in aqueous solution by the admixture of CAUSYTH® to an aqueous solution of the appropriate polyhydroxy-amine. The aqueous solution may be lyophilised in conventional manner to obtain a solid residue comprising the water-soluble complex.

The complexes of the present invention are freely soluble in, and stable in, water, forming aqueous solutions generally having a pH in the range 6.5 to 6.8, suitable for pharmaceutical use. Furthermore aqueous solutions of the complexes are easily lyophilised, forming a solid lyophilisate capable of being reconstituted in water into an injectible solution, as is the case with the great majority of medicaments, such as vitamins, antibiotics and therapeutic salts, used with vehicles in injectible solutions.

The complexes of the invention, when injected, give rise to no toxic phenomena, are well tolerated by sick persons and show the curative properties of CAUSYTH ® particularly strongly, thus constituting an anti-influenzal and anti-rheumatic medicament, having a rapid effect in reducing or eliminating hyperthermia in influenzal and rheumatic condition and having a quick-acting analgesic effect.

The complexes of the invention may be administered as pharmaceutical compositions in admixture with pharmaceutically acceptable carriers or diluents, in particular as aqueous solutions, either parenterally, intravenously or intramuscularly. A suitable average daily dose is 1 to 2 gms.

One of the advantages of the preparations of the invention is that they make it possible to treat cases of acute articular rheumatism, rheumatoid arthritis, influenza and similar feverish conditions, by a therapy having a particularly rapid effect. This rapidity of action is not obtained in the same degree by the use of the medicament by the enteral method.

Another advantage of the preparations of the invention is that improved effectiveness and rapidity and excellent results may be obtained by the use of the medicament by the parenteral method as compared with the use thereof by the oral or rectal method.

A further advantage of the preparations of the invention is represented by the possibility of treating cases in which use by the oral method is impossible because of particular gastrointestinal conditions of the patient.

Another advantage of the preparations of the invention is that they enable rectal use to be avoided in all cases where this not advisable, such as, for example, cases of haemorrhoids and anal fistulae.

Another advantage of the preparations of the invention is that they obviate the use of the medicament by the oral method in all those cases where this mehod of use could, by way of excepion, prove to be inappropriate, as in cases of nausea, digestive difficulties, sluggishness or pyrosis.

An additional advantage of the preparations of the invention is that CAUSYTH ® is made available in a lyophilised form, if required in admixture with other co-adjuvant products such as vitamins, hormones, anti-inflammatory agents or antibiotics, the CAUSYTH® being immediately reconstitutable, in aqueous medium or in physiological solution, into an injectible solution.

The following Examples are intended solely to illustrate the preparations of the invention and the tests carried out with the said preparations.

EXAMPLE 1.

950 c.c. of distilled water are boiled for 10 minutes in a graduated 1000 cc flask. After boiling, the water is allowed to cool to a temperature of about 40°C., 40 g of perfectly pure methyl-glucamine are added, stirring is carried out until dissolution is complete and 100 g of CAUSYTH® in powder form are then added. Further stirring is carried out for a few minutes so as to obtain a perfect and complete solution. As the CAUSYTH® dissolves, the solution has a yellow coloration. A check is made on the pH value which is normally 6.5. A further 2—4 g of methylglucamine are added so that the pH value increases and becomes equal to 6.7—6.8. The solution is then filtered by means of CM 100 " Ginori " filters (Berkefeld type) and the filtered

solution, which is perfectly clear, is put into ampoules. The ampoules are sterilised by means of steam under reflux.

A fraction of the solution, after an accelerated ageing test (24 hours at 110°C.) by means of acidification, shows precipitation of the CAUSYTH(R) and this is recovered in exactly the quantity calculated.

EXAMPLE 2.

A solution of CAUSYTH(R) is prepared as specified in Example 1, substutiting 36 g of aminoglycerine for the methylglucamine.

EXAMPLE 3.

A solution of CAUSYTH(R) is prepared as specified in Example 1, substituting 38 g of glucosamine for the methylglucamine.

EXAMPLE 4.

A solution of CAUSYTH(R) is prepared as specified in Example 1, substituting 40 g of glucamine for the methylglucamine.

EXAMPLE 5.

A solution of CAUSYTH(R) is prepared as specified in Example 1 and this is placed in ampoules for lyophilisation. Lyophilisation is carried out normally, a solid residue having a crystalline appearance and a yellow coloration being obtained. This residue dissolves rapidly in an aqueous medium, yielding a solution the characteristics of which are identical to those described in Example 1.

EXAMPLE 6.

A solution of CAUSYTH(R) is prepared as specified in Example 1, water-soluble vitamins, in particular vitamins of group B, such as thiamine hydrochloride, riboflavin, nicotinic acid and vitamin B12, being added; then, in order to ensure perfect long-term preservation of the vitamins, this solution is lyophilised and in this way there is obtained a solid residue which is perfectly reconstitutable in an aqueous medium, the solution obtained being identical to the initial solution.

EXAMPLE 7.

The lyophilised product described in Example 5 is reconstituted with a vitamin solution containing vitamins B1, B2, B6, B12, nicotinamide and vitamin C in therapuetic doses. This solution is injectable by the parenteral method.

EXAMPLE 8.

The solution obtained in Example 1 is injected endoperitoneally into white mice by the Lichtfield and Wilcox method in order to determine the degree of acute toxicity. The LD 50 is 500 mg/kg of body weight.

EXAMPLE 9.

The solution obtained in Example 1 is injected endoperitoneally into white mice in a daily dose of 25 mg/kg for a period of 6 weeks.

No disturbance in growth, nor any change in the leucocytic formula or any anatomopathological deterioration is observed.

EXAMPLE 10.

The solution obtained in Example 1 is injected into white mice suffering from phlogosis caused by endoperitoneal dextran or formaldehyde; the antiphlogistic activity as regards the piezometric test is distinct and immediate.

In rats which have been rendered hyperthermic by administration of yeast by Maren's method (Journal of Pharmacology and Applied Therapeutics, 101,313 (1951)), the antithermic activity is intense and immediate.

EXAMPLE 11.

The solution obtained in Example 1 has been tested in 32 clinical cases comprising various feverish and rheumatic syndromes.

By employing this by intravenous injection in an average dose of 1—2 g per day, an excellent antipyretic and analgesic action was obtained from the first or second day of the treatment.

The many controls carried out did not reveal any toxic or secondary symptoms.

WHAT WE CLAIM IS:—

1. A water-soluble complex of 1,5 - dimethyl - 4 - dimethylamino - 2 - phenyl-3 - isopyrazolone 8 - hydroxy - quinoline - 5 - sulphonate and an aliphatic polyhydroxy-amine or an aliphatic cyclic polyhydroxyamine (as hereinbefore defined).

2. A complex as claimed in claim 1 in which the polyhydroxy - amine is amino-glycerine, methylaminoglycerine, glucamine, methylglucamine, glucosamine or methyl-glucosamine.

3. A complex as claimed in claim 1 or 2 substantially as hereinbefore described and exemplified.

4. A pharmaceutical composition, useful in particular against influenza and febrile and rheumatic conditions, containing a complex as claimed in any of claims 1 to 3 in admixture with a pharmaceutically acceptable diluent or carrier.

5. An aqueous solution containing a water-soluble complex as claimed in any of claims 1 to 3.

6. An aqueous solution as claimed in claim 5 having a pH between 6.5 and 6.8.

7. An aqueous solution as claimed in claim 5 or 6 additionally containing one or more water-soluble vitamins, hormones or antibiotics.

8. A lyophilisate of an aqueous solution claimed in any of claims 5 to 7.

9. A pharmaceutical composition containing a complex as claimed in any of claims 1 to 3 substantially as hereinbefore described and exemplified.

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